

Aminoalkylation of Cyclic and Acyclic Alkyl Vinyl Ethers

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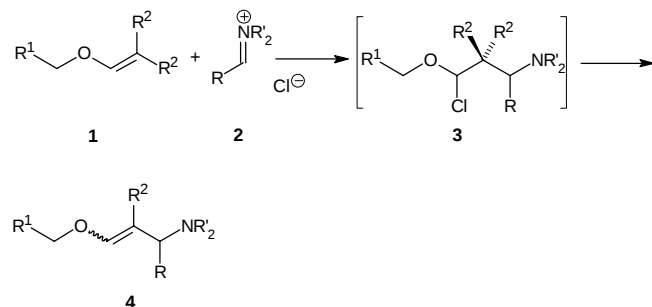
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Abstract. The aminoalkylation of cyclic and acyclic alkyl vinyl ethers from inexpensive starting materials yields Mannich bases **4** and **10**. Preformed and *in situ* generated iminium salts are used under mild reaction conditions. In some cases it is possible to isolate the α -halogenated 1,3-amino

ethers **3** which have so far only ever been assumed to exist. Furthermore, the preparation of the already known 1-benzotriazolyl-3-aminoalkyl ethers **6** and **9** using this methodology is also successful.

The aminoalkylation of carbonyl compounds with ternary iminium salts is of general interest [1–9]. Recently, we have disclosed that the aminoalkylation of ketones, enamines, imines (derivatives of aldehydes, cyclic or acyclic ketones) and aromatic compounds provides the corresponding Mannich bases in excellent yields and diastereoselectivities [1, 2, 8–11]. By contrast, only a few other types of nucleophiles have been treated with ternary iminium salts containing alkyl, aryl and carboxylate groups, presumably because of the difficult preparation and handling of these compounds [12–14].

**1a:** $R^1 = \text{Me}$, $R^2 = \text{H}$ **1b:** $R^1 = \text{H}$, $R^2 = \text{Me}$

2, 3, 4	R^1	R^2	R	R'	R'	X
a	Me	H	H	Me	Me	Cl
b	Me	H	CO ₂ Et	Me	Me	Cl
c	Me	H	Ph	Me	Me	Cl
d	Me	H	H	Me	Me	Bt ^a)
e	Me	H	CO ₂ Et	Me	Me	Bt ^a)
f	Me	H	Ph	Me	Me	Bt ^a)

^a) Bt = Benzotriazole**Scheme 1** Aminoalkylation of acyclic alkyl vinyl ethers **1** with ternary iminium salts **2**

Böhme and Wagner have already described the aminomethylation of the acyclic alkyl vinyl ethers (**1a,b**) with preformed methylene iminium salts (**2a**) ($R = \text{H}$ and $X = \text{Cl}$) [15]. Only in those cases where the dehydrohalogenation is impossible (*e.g.* **1b**: $R^1 = \text{H}$, $R^2 = \text{Me}$), were they able to isolate the α -halogenated ether **3** (Scheme 1).

Katritzky *et al.* reported that the ethyl vinyl ether **1a** can be aminoalkylated by 1-(α -aminoalkyl)benzotriazoles **5** ($R = \text{H}$, Ph) by heating (120 °C) to give quantitatively a mixture of the benzotriazol-1-yl (**6**) and -2-yl (**7**) adducts ($R = \text{Ph}$, $\text{NR}'_2 = \text{morpholine}$: **6** : **7** = 1 : 1, *syn*-**6** : *anti*-**6** = 1 : 1, *syn*-**7** : *anti*-**7** = 1 : 1) [16] (Scheme 2). These compounds are easily converted into the 1,3-amino ethers by treatment with alkyl magnesium bromide or lithium aluminium hydride [16].

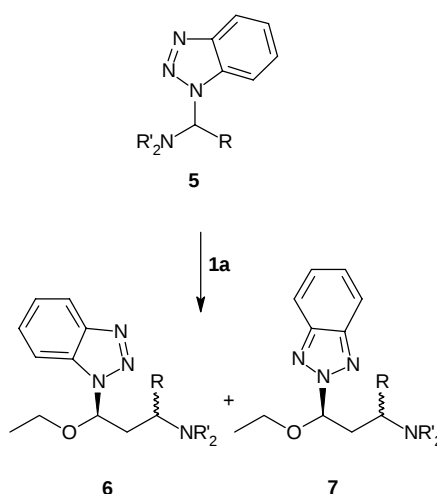
**Scheme 2** Aminoalkylation of acyclic alkyl vinyl ethers **1** with 1-(aminoalkyl)-benzotriazoles **5**

Table 1 Aminoalkylation of ethyl vinyl ether (**1a**) with ternary iminium salts **2**

Entry	Iminium-Salt 2	Method ^{a)}	R	R'	R'	X	Product	Yield (%)
1	2a	A	H	Me	Me	Cl	3a	84
2	2b	B	CO ₂ Et	Me	Me	Cl	4b	87
3	2c	A	Ph	Me	Me	Cl	3c	65
4	2d	C	H	Me	Me	Bt [18]	6d	85
5	2e	C	CO ₂ Et	Me	Me	Bt [18]	6e ^{b)}	81
6	2f	C	Ph	Me	Me	Bt [18]	6f ^{c)}	77

^{a)} See experimental section. ^{b)} Two diastereoisomers of **6e** in the ratio 1 : 1. ^{c)} Two diastereoisomers of **6f** in the ratio 1 : 1.

This paper describes a very promising improvement and extension of these methodologies, namely the reaction of alkyl vinyl ethers with preformed (R = H, Ph; X = Cl; method A) and *in situ* generated iminium salts **2** (R = CO₂Et, X = Cl, method B; R = H, Ph, CO₂Et; X = Bt [18], method C) under mild reaction conditions [15–17] (Scheme 1). The results are shown in Table 1.

The reaction with the iminium salts **2a–c** (R = H, Ph, CO₂Et; X = Cl) provides the aminoalkylated products in good yields. In contrast to Böhme and Wagner [15] we were able to isolate the α -halogenated ethers **3a** and **3c** respectively, presumably because of the mild reaction conditions. By contrast, **2b** affords the eliminated products *E*-**4b** and *Z*-**4b**. The characteristic

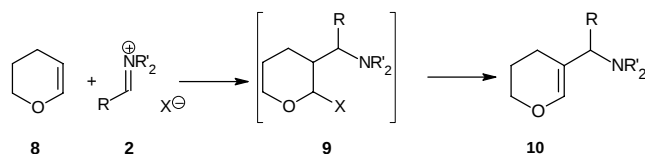
CH=CH–O signals in the ¹H NMR spectra of the crude product ($\delta_E = 6.42$ ppm, d, $J = 12.7$ Hz and $\delta_Z = 6.14$ ppm, d, $J = 5.9$ Hz) allow to determine the ratio of the *E* : *Z* isomers as being 5 : 1.

Probably, the mild reaction conditions also lead to different results in comparison with those of Katritzky [16]. The use of the iminium salt **2d** produces the benzotriazol-1-yl-derivate **6d**. The generated iminium salts **2e** and **2f** yield the two diastereomeric benzotriazol-1-yl adducts *syn*- and *anti*-**6e** and *syn*- and *anti*-**6f**, respectively, in a ratio of 1 : 1. The benzotriazol-2-yl-isomer **7** was not detected in the crude product.

Former investigations indicated that cyclic alkyl vinyl ethers such as dihydropyran (**8**) react with methylene iminium salts (**2a**) in the same way as described before (Scheme 3) [15].

In this case, too, we tried to simplify the reaction conditions and to increase the diversity of the products by using various substituted iminium salts **2**. The results are summarized in Table 2.

Our investigations have shown that the different methodologies to generate the iminium salts **2** and the resulting reaction conditions lead to a variety of interesting synthetic building blocks. The reaction of **2a–b** and **8** produces the expected compounds **10a–b** in good yields, whereas **2c** is not sufficiently electrophilic for the aminoalkylation of **8**. Under similar conditions **2d** and **2e** add to **8** producing two diastereoisomers **9d** (5 : 1) and **9e** (3 : 1), respectively. The *syn*- and *anti*-configuration of the benzotriazol-1-yl isomer was assigned by comparison of the NMR data with related compounds



	R	R'	R'	X
a	H	Me	Me	Cl
b	CO ₂ Et	Me	Me	Cl
c	Ph	Me	Me	Cl
d	H	Me	Me	Bt ^{a)}
e	CO ₂ Et	Me	Me	Bt ^{a)}
f	Ph	Me	Me	Bt ^{a)}

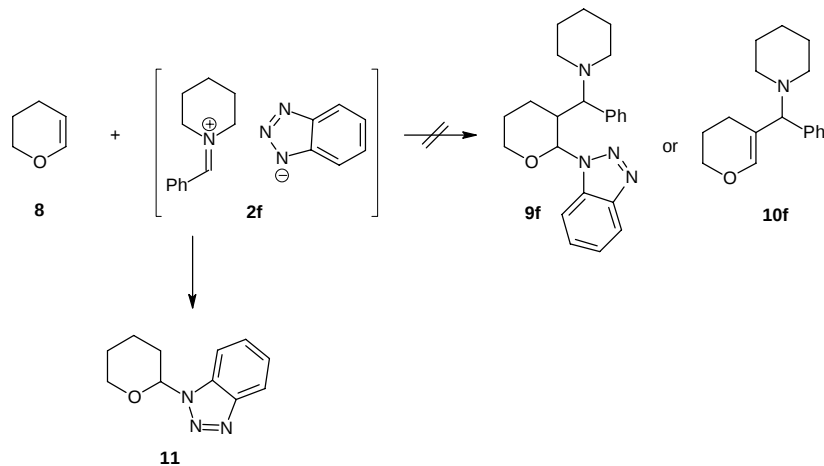
^{a)} Bt = Benzotriazole

Scheme 3 Aminoalkylation of dihydropyran **8** with ternary iminium salts **2****Table 2** Aminoalkylation of dihydropyran (**8**) with ternary iminium salts **2**

Entry	Iminium-Salt 2	Method ^{a)}	R	R'	R'	X	Product	Yield (%)
1	2a	A	H	Me	Me	Cl	10a	96 [15]
2	2b	B	CO ₂ Et	Me	Me	Cl	10b	89
3	2c	A	Ph	Me	Me	Cl	–	–
4	2d	C	H	Me	Me	Bt [18]	9d ^{b)}	90
5	2e	C	CO ₂ Et	Me	Me	Bt [18]	9e ^{c)}	85
6	2f	C	Ph	Me	Me	Bt [18]	11 ^{d)}	83

^{a)} see experimental section. ^{b)} Diastereomeric ratio 5 : 1. ^{c)} Diastereomeric ratio 3 : 1. ^{d)} Adduct of the benzotriazolate-anion and dihydropyran (**8**).

[16]. By contrast, the reaction of **2f** and **8** yields neither the expected product **9f** nor **10f**. Instead, **11**, the adduct of the benzotriazolate anion and **8**, was isolated in a yield of 83 % (Scheme 4).



Scheme 4 Formation of the 1-(tetrahydro-pyran-2-yl)-1H-benzotriazole (**11**)

In summary, the diversity in the chemistry of Mannich bases is extended by the use of ternary iminium salts for the aminoalkylation of cyclic and acyclic vinyl ethers. Our method requires inexpensive and readily available chemicals and can be applied to a wide range of substrates. Furthermore, there are many notable prospects. The mild reaction conditions allow some results new to the literature. In some cases we are able to isolate the α -substituted 1,3-amino ether (*i.e.* **3a** and **3c**). The use of 1-(α -aminoalkyl)-benzotriazoles in our methodology generates the benzotriazol-1-yl adducts as a mixture of only two diastereoisomers [16].

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Experimental

Anhydrous THF was freshly distilled from potassium under argon. Column chromatography on silica gel was performed with Merck silica gel 60 (0.040/0.063 mm). ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 200 or a Bruker AMX 300 spectrometer, using TMS as internal standard. GC/MS data were obtained from a Finnigan MAT Magnum System 240 and MS data from a VG Fisons Autospec. Elemental analyses were performed on a Perkin Elmer Elemental Analyser. Satisfactory microanalyses were obtained for the new compounds, **3a**, **3c**, **4b**, **6d–f**, **9d–e**, **10b** and **11**: C % 0.34, H % 0.28, N % 0.19.

128.82, 129.07, 129.39 (d, Ar), 134.84 (s, Ar). – GC/MS (EI/80 eV) m/z (%) = 206 (2), 134 (100).

$\text{C}_{13}\text{H}_{20}\text{NOCl}$	Calcd.:	C 64.59	H 8.33	N 5.79
(241.74)	Found:	C 64.25	H 8.05	N 5.61.

Method A

The reactions were conducted under argon. To solutions of **1** and **8**, respectively (2 mmol) in anhydrous CH_2Cl_2 (3 mL) the preformed iminium salt **2a** [15] or **2c** [19, 20] was added in one portion. After stirring overnight, HCl (6N) was added, and the aqueous layer was washed with Et_2O several times. The aqueous layer was basified by the addition of NH_3 and extracted with CH_2Cl_2 (3×50 mL). The organic layer was dried over Na_2SO_4 , and the solvent was removed *in vacuo*. The aminoalkylated alkyl vinyl ethers, **3a**, **3c** and **10a** were isolated as yellowish oily products without further purification.

(3-Chloro-3-ethoxy-propyl)dimethylamine (**3a**)

^1H NMR (200 MHz, CDCl_3) δ /ppm = 1.19 (t, 3H, J = 7.1 Hz, $\text{CH}_3\text{CH}_2\text{O}$), 1.72–1.83 (m, 1H, $\text{N}(\text{CH}_3)_2\text{CH}_2\text{CH}_2$), 2.21 (s, 6H, $\text{N}(\text{CH}_3)_2$), 2.26–2.42 (m, 1H, $\text{N}(\text{CH}_3)_2\text{CH}_2\text{CH}_2$), 3.41–3.77 (m, 4H, $\text{CH}_3\text{CH}_2\text{O}$, $\text{N}(\text{CH}_3)_2\text{CH}_2\text{CH}_2$), 4.56 (dd, 1H, J = 2.2 Hz, J = 5.7 Hz, OCHCl). – ^{13}C NMR (75 MHz, CDCl_3) δ /ppm = 15.69 (q, $\text{CH}_3\text{CH}_2\text{O}$), 32.31 ($\text{N}(\text{CH}_3)_2\text{CH}_2\text{CH}_2$), 45.91 (q, $\text{N}(\text{CH}_3)_2$), 55.57 (t, $\text{N}(\text{CH}_3)_2\text{CH}_2\text{CH}_2$), 61.50 (t, $\text{CH}_3\text{CH}_2\text{O}$), 101.92 (d, OCHCl).

$\text{C}_7\text{H}_{16}\text{NOCl}$	Calcd.:	C 50.78	H 9.73	N 8.46
(165.58)	Found:	C 51.07	H 9.45	N 8.29.

(3-Chloro-3-ethoxy-1-phenyl-propyl)-dimethyl-amine (**3c**)

^1H NMR (200 MHz, CDCl_3) δ /ppm = 1.15 (t, 3H, J = 7.2 Hz, $\text{CH}_3\text{CH}_2\text{O}$), 1.83–1.96 (m, 1H, $\text{N}(\text{CH}_3)_2\text{CHCH}_2\text{CH}$), 2.19 (s, 6H, $\text{N}(\text{CH}_3)_2$), 2.25–2.36 (m, 1H, $\text{N}(\text{CH}_3)_2\text{CHCH}_2\text{CH}$), 3.28–3.41 (m, 3H, $\text{CH}_3\text{CH}_2\text{O}$, $\text{N}(\text{CH}_3)_2\text{CH}$), 4.22 (dd, 1H, J = 4.3 Hz, J = 7.4 Hz, OCHCl), 7.23–7.64 (m, 5H, Ph). – ^{13}C NMR (50 MHz, CDCl_3) δ /ppm = 15.76 (q, $\text{CH}_3\text{CH}_2\text{O}$), 37.51 (t, $\text{N}(\text{CH}_3)_2\text{CHCH}_2$), 42.88 (q, $\text{N}(\text{CH}_3)_2$), 61.61 (t, $\text{CH}_3\text{CH}_2\text{O}$), 66.91 (d, $\text{N}(\text{CH}_3)_2\text{CH}$), 101.60 (d, OCHCl),

(5,6-Dihydro-4H-pyran-3-ylmethyl)-dimethyl-amine (10a)

^1H NMR (300 MHz, CDCl_3) δ /ppm = 1.89–1.93 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 2.56–2.68 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 2.80 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.55 (s, 2H, $\text{CH}_2\text{N}(\text{CH}_3)_2$), 3.90–4.01 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 6.67 (s, 1H, CCHO). – ^{13}C NMR (75 MHz, CDCl_3) δ /ppm = 21.23 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 22.53 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 41.62 (q, $\text{N}(\text{CH}_3)_2$), 61.16 (t, $\text{CH}_2\text{N}(\text{CH}_3)_2$), 65.58 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 102.65 (s, CCHO), 147.99 (d, CCHO).

$\text{C}_8\text{H}_{15}\text{NO}$ Calcd.: C 68.03 H 10.70 N 9.92
(141.12) Found: C 68.27 H 10.51 N 10.09.

Method B

The reactions were conducted under argon. A solution of di-(piperidin-1-yl) ethyl acetate [2] (2 mmol) in anhydrous CH_2Cl_2 (3 mL) was cooled to 0 °C. Acetyl chloride (0.14 mL, 2 mmol) was added in one portion to generate the iminium salt **2b**. After stirring the mixture for 1 h at 0 °C, alkyl vinyl ether **1a** or **8** was added, and the solution was stirred overnight. The crude products **4b** and **10b**, respectively, were isolated as described above. The residue also contained 1-acetylpiperidine [2]. The product was purified by column chromatography (silica gel, CH_2Cl_2 : MeOH = 98 : 2).

Ethyl 4-Ethoxy-2-(piperidin-1-yl)but-3-enoate (4b)

E-Configuration (major product): – ^1H NMR (200 MHz, CDCl_3) δ /ppm = 6.42 (d, 1H, J = 12.7 Hz, OCHCH). – ^{13}C NMR (50 MHz, CDCl_3) δ /ppm = 14.53, 14.87 (2 q, $\text{CH}_3\text{CH}_2\text{O}$, $\text{CH}_3\text{CH}_2\text{CO}_2$), 26.13, 26.92 (2 t, $\text{N}(\text{CH}_2)_5$), 52.13 (t, $\text{N}(\text{CH}_2)_5$), 60.89, 65.07 (2 t, $\text{CH}_3\text{CH}_2\text{O}$, $\text{CH}_3\text{CH}_2\text{CO}_2$), 69.95 (d, $\text{CHN}(\text{CH}_2)_5$), 99.62 (OCHCH), 150.60 (OCHCH) 172.59 (s, $\text{CH}_3\text{CH}_2\text{CO}_2$). – GC/MS (EI/80 eV) m/z (%) = 242 (13) [$\text{M}^+ + 1$], 168 (100), 140 (27), 122 (20), 84 (16). – *Z*-Configuration (minor product): ^1H NMR (200 MHz, CDCl_3) δ /ppm = 6.14 (d, 1H, J = 5.9 Hz, OCHCH). – GC/MS (EI/80 eV) m/z (%) = 242 (11) [$\text{M}^+ + 1$], 195 (2), 168 (100), 157 (4), 122 (24), 84 (49).

$\text{C}_{13}\text{H}_{23}\text{NO}_3$ Calcd.: C 64.71 H 9.60 N 5.80
(241.31) Found: C 64.42 H 9.85 N 5.62.

(5,6-Dihydro-4H-pyran-3-ylmethyl)-piperidin-1-yl-acetic acid ethyl ester (10b)

^1H NMR (300 MHz, CDCl_3) δ /ppm = 1.26 (t, 3H, J = 7.1 Hz, $\text{CH}_3\text{CH}_2\text{CO}_2$), 1.29–1.49 (m, 2H, $\text{N}(\text{CH}_2)_5$), 1.53–1.62 (m, 4H, $\text{N}(\text{CH}_2)_5$), 1.72–1.98 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 2.00–2.16 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 2.29–2.42 (m, 4H, $\text{N}(\text{CH}_2)_5$), 3.16 (s, 1H, CCHCO_2), 3.86–4.01 (m, 2H, $\text{CH}_3\text{CH}_2\text{CO}_2$), 4.10–4.31 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 6.48 (s, 1H, CCHO). – ^{13}C NMR (75 MHz, CDCl_3) δ /ppm = 13.94 (q, $\text{CH}_3\text{CH}_2\text{CO}_2$), 19.64 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 21.89 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 24.21 (1t, $\text{N}(\text{CH}_2)_5$), 25.42 (2 t, $\text{N}(\text{CH}_2)_5$), 51.89 (2 t, $\text{N}(\text{CH}_2)_5$), 60.10 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 65.64 (t, $\text{CH}_3\text{CH}_2\text{CO}_2$), 73.05 (d, CCHCO_2), 108.34 (s, CCHO), 143.77 (d, CCHCO), 171.23 (s, $\text{CH}_3\text{CH}_2\text{CO}_2$).

$\text{C}_{13}\text{H}_{23}\text{NO}_3$ Calcd.: C 64.69 H 9.60 N 5.81
(241.17) Found: C 64.35 H 9.88 N 5.69.

Method C

The reactions were conducted under argon. A solution of the 1-(α -aminoalkyl)benzotriazole [10, 16] (2 mmol) in anhy-

drous THF (10 mL) was cooled to –80 °C. TiCl_4 (4 mmol, 0.45 mL) was then added carefully [10]. After stirring the mixture for 1 h at this temperature, the alkyl vinyl ether **1a** or **8** was added in one portion, and the temperature was allowed to rise to 0 °C overnight. The mixture was poured into saturated NaHCO_3 -solution (50 mL) and the crude product extracted with CH_2Cl_2 several times. The 1-benzotriazolyl-3-aminoalkyl ethers **6d–f** and **9d–e**, respectively, or the 1-benzotriazolyl ether **11** were isolated as yellowish oily products without further purification.

[3-(Benzotriazol-1-yl)-3-ethoxypropyl]dimethylamine (6d)

^1H NMR (200 MHz, CDCl_3) δ /ppm = 1.14 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.21 (s, 6H, $\text{N}(\text{CH}_3)_2$), 2.28–2.49 (m, 2H, OCHCH_2), 3.21–3.85 (m, 4H, $\text{CH}_3\text{CH}_2\text{O}$, $\text{N}(\text{CH}_3)_2\text{CH}_2$), 6.23–6.78 (m, 1H, OCHBt), 7.31–7.58 (m, 2H, Bt), 7.80 (d, 1H, J = 7.9 Hz, Bt), 8.08 (d, 1H, J = 7.9 Hz, Bt). – ^{13}C NMR (50 MHz, CDCl_3) δ /ppm = 15.09 (q, $\text{CH}_3\text{CH}_2\text{O}$), 33.29 (t, OCHCH_2), 45.75 (q, $\text{N}(\text{CH}_3)_2$), 55.10 (t, $\text{N}(\text{CH}_3)_2\text{CH}_2$), 65.02 (t, $\text{CH}_3\text{CH}_2\text{O}$), 89.11 (d, OCHBt), 111.52, 120.42, 124.62, 127.87 (4 d, Bt), 131.88, 147.06 (2 s, Bt).

$\text{C}_{13}\text{H}_{20}\text{N}_4\text{O}$ Calcd.: C 62.88 H 8.11 N 22.56
(248.31) Found: C 63.16 H 8.34 N 22.72.

4-Benzotriazol-1-yl-4-ethoxy-2-piperidin-1-yl-butyric acid ethyl ester (6e)

both diastereoisomers: ^1H NMR (300 MHz, CDCl_3) δ /ppm = 1.03–4.31 (m, 23H, $\text{CH}_3\text{CH}_2\text{O}$, $\text{CH}_3\text{CH}_2\text{O}$, $\text{CH}_3\text{CH}_2\text{CO}_2$, $\text{CH}_3\text{CH}_2\text{CO}_2$, OCHCH_2 , $\text{N}(\text{CH}_2)_5$, $\text{CHN}(\text{CH}_2)_5$), 6.12–6.52 (m, 1H, OCHBt), 7.31–7.55 (m, 2H, Bt), 7.78 (d, 1H, J = 8.1 Hz, Bt), 8.07 (d, 1H, J = 8.1 Hz, Bt). – both diastereoisomers: ^{13}C NMR (75 MHz, CDCl_3) δ /ppm = 14.80, 14.93 (q, $\text{CH}_3\text{CH}_2\text{O}$, $\text{CH}_3\text{CH}_2\text{CO}_2$), 24.85, 25.95, 26.92, 34.37 (4 t, $\text{N}(\text{CH}_2)_5$, OCHCH_2), 51.03 (t, $\text{N}(\text{CH}_2)_5$), 65.92, 65.15 (d, $\text{CHN}(\text{CH}_2)_5$), 68.27 (t, $\text{CH}_3\text{CH}_2\text{CO}_2$), 88.21, 89.50 (d, OCHBt), 111.34, 120.33, 124.53, 127.76 (4 d, Bt), 131.65, 147.11 (2 s, Bt), 172.47, 173.13 (s, $\text{CH}_3\text{CH}_2\text{CO}_2$). – GC/MS (EI/80 eV) m/z (%) = 361 (1) [$\text{M}^+ + 1$], 287 (10), 241 (10), 212 (8), 287 (100).

$\text{C}_{19}\text{H}_{28}\text{N}_4\text{O}_3$ Calcd.: C 63.26 H 7.82 N 15.54
(360.43) Found: C 63.57 H 7.67 N 15.38.

1-(1-Ethoxy-3-phenyl-3-piperidin-1-yl-propyl)-1H-benzotriazole (6f)

both diastereoisomers: ^1H NMR (50 MHz, CDCl_3) δ /ppm = 1.09–3.96 (m, 18H, $\text{CH}_3\text{CH}_2\text{O}$, $\text{CH}_3\text{CH}_2\text{O}$, OCHCH_2 , $\text{N}(\text{CH}_2)_5$, $\text{CHN}(\text{CH}_2)_5$), 5.98* (br s, 1H, OCHBt), 6.30 (br s, 1H, OCHBt), 7.15–7.51 (m, 7H, Bt, Ph), 7.78 (d, 1H, J = 8.0 Hz, Bt), 8.11 (d, 1H, J = 8.0 Hz, Bt). – both diastereoisomers: ^{13}C NMR (50 MHz, CDCl_3) δ /ppm = 15.08, 21.56 (q, $\text{CH}_3\text{CH}_2\text{O}$), 24.94, 25.99, 26.78, 37.11, 37.77, 50.83, 51.14 (5 t, $\text{N}(\text{CH}_2)_5$, OCHCH_2), 64.71, 64.89 (d, $\text{N}(\text{CH}_2)_5$), 65.77, 66.14 (d, $\text{CHN}(\text{CH}_2)_5$), 68.31 (t, $\text{CH}_3\text{CH}_2\text{O}$), 87.39, 88.98 (d, OCHBt), 111.65, 120.31, 124.48, 127.80 (4 d, Bt), 134.82, 146.92 (2 s, Bt).

$\text{C}_{22}\text{H}_{28}\text{N}_4\text{O}$ Calcd.: C 72.44 H 7.74 N 15.37
(364.46) Found: C 72.18 H 7.51 N 15.56.

(2-Benzotriazol-1-yl-tetrahydropyran-3-ylmethyl)-dimethylamine (9d)

major diastereoisomer: ^1H NMR (200 MHz, CDCl_3) δ /ppm = 1.22–2.81 (m, 5H, $\text{OCH}_2\text{CH}_2\text{CH}_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2$, CHCH_2

$\text{N}(\text{CH}_3)_2$, 2.00 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.84–4.20 (m, 4H, $\text{CH}_2\text{N}(\text{CH}_3)_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 5.85 (d, 1H, $J = 7.3$ Hz, OCH-Bt), 7.29–7.53 (m, 2H, Bt), 7.71 (d, 1H, $J = 8.2$ Hz, Bt), 8.03 (d, 1H, $J = 8.2$ Hz, Bt). – ^{13}C NMR (50 MHz, CDCl_3) $\delta/\text{ppm} = 24.26$ (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 26.73 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 36.72 (2 q, $\text{N}(\text{CH}_3)_2$), 46.19 (d, $\text{CHCH}_2\text{N}(\text{CH}_3)_2$), 60.98 (t, $\text{CH}_2\text{N}(\text{CH}_3)_2$), 67.15 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 88.63 (d, OCHBt), 111.33, 120.26, 124.54, 127.89 (4 d, Bt), 132.87, 146.71 (2 s, Bt). – minor diastereoisomer: ^{13}C NMR (50 MHz, CDCl_3) $\delta/\text{ppm} = 22.74$ (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 26.73 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 36.72 (2 q, $\text{N}(\text{CH}_3)_2$), 44.91 (d, $\text{CHCH}_2\text{N}(\text{CH}_3)_2$), 66.03 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 88.63 (d, OCHBt), 110.91, 120.26, 124.54, 127.75 (4 d, Bt), 132.87, 144.85 (2 s, Bt). – GC/MS (EI/80 eV) m/z (%) = 141 (18) [$\text{M}^+ - \text{HBt}$], 97 (58), 84 (21), 58 (17), 49 (100).

$\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}$ Calcd.: C 64.33 H 7.71 N 21.45
(261.18) Found.: C 64.00 H 7.96 N 21.58.

(2-Benzotriazol-1-yl-tetrahydropyran-3-yl)-piperidin-1-yl-acetic acid ethyl ester (9e)

both diastereoisomers: ^1H NMR (300 MHz, CDCl_3) $\delta/\text{ppm} = 1.04$ – 2.64 (m, 14H, $\text{CH}_3\text{CH}_2\text{CO}_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2$, $\text{N}(\text{CH}_2)_5$, OCHCH), 3.18–4.24 (m, 9H, $\text{OCH}_2\text{CH}_2\text{CH}_2$, $\text{N}(\text{CH}_2)_5$, OCHCH, $\text{CH}_3\text{CH}_2\text{CO}_2$), 6.04* (br s, 1H, OCHBt), 6.38 (br s, 1H, OCHBt), 7.28–7.50 (m, 2H, Bt), 7.75 (br s, 1H, Bt), 8.08 (br s, 1H, Bt). – major diastereoisomer: ^{13}C NMR (75 MHz, CDCl_3) $\delta/\text{ppm} = 14.45$ (q, $\text{CH}_3\text{CH}_2\text{CO}_2$), 21.76, 22.21, 24.14, 25.97 (4 t, $\text{OCH}_2\text{CH}_2\text{CH}_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2$, $\text{N}(\text{CH}_2)_5$), 33.75 (d, OCHCH), 50.85 (t, $\text{N}(\text{CH}_2)_5$), 63.74, 68.55 (2 t, $\text{OCH}_2\text{CH}_2\text{CH}_2$, $\text{CH}_3\text{CH}_2\text{CO}_2$), 85.13 (d, OCHBt), 110.81, 119.58, 123.85, 127.18 (4 d, Bt), 132.95, 146.11 (2 s, Bt), 169.10 ($\text{CH}_3\text{CH}_2\text{CO}_2$). – minor diastereoisomer: ^{13}C NMR (75 MHz, CDCl_3) $\delta/\text{ppm} = 14.45$ (q, $\text{CH}_3\text{CH}_2\text{CO}_2$), 21.38, 24.70, 29.06 (3 t, $\text{OCH}_2\text{CH}_2\text{CH}_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2$, $\text{N}(\text{CH}_2)_5$), 59.87 ($\text{N}(\text{CH}_2)_5$), 63.74, 68.55 (2 t, $\text{OCH}_2\text{CH}_2\text{CH}_2$, $\text{CH}_3\text{CH}_2\text{CO}_2$), 85.44 (d, OCHBt), 110.88, 119.69, 123.85, 127.18 (4 d, Bt), 132.95, 146.11 (2 s, Bt), 169.10 ($\text{CH}_3\text{CH}_2\text{CO}_2$). – both diastereoisomers: GC/MS (EI/80 eV) m/z (%) = 254 (2) [$\text{M}^+ - \text{HBt}$], 208 (2), 180 (100), 152 (48).

$\text{C}_{20}\text{H}_{28}\text{N}_4\text{O}_3$ Calcd.: C 64.48 H 7.57 N 15.05
(372.24) Found.: C 64.29 H 7.85 N 14.95.

1-(Tetrahydropyran-2-yl)-1H-benzotriazole (11)

^1H NMR (200 MHz, CDCl_3) $\delta/\text{ppm} = 1.66$ – 1.91 (m, 3H, $\text{OCH}_2\text{CH}_2\text{CH}_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 2.03–2.28 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$, OCHCH), 2.49–2.71 (m, 1H, OCHCH), 3.69–3.97 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 6.01 (dd, 1H, $J = 2.6$ Hz, $J = 8.3$ Hz, OCHBt), 7.31–7.50 (m, 2H, Bt), 7.73 (d, 1H, $J = 8.2$ Hz), 8.04 (d, 1H, $J = 8.2$ Hz, Bt). – ^{13}C NMR (50 MHz, CDCl_3) $\delta/\text{ppm} = 22.05$ (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 25.29, 29.69 (2 t,

$\text{OCH}_2\text{CH}_2\text{CH}_2$, OCHCH), 67.32 (t, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 86.04 (d, OCHBt), 111.52, 120.54, 124.54, 127.86 (4 d, Bt), 132.82, 146.70 (2 s, Bt).

$\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}$ Calcd.: C 64.99 H 6.44 N 20.68
(203.12) Found.: C 65.31 H 6.24 N 20.84.

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